

REMARKS

The claims are 12-16. The non-elected claims have been canceled without prejudice to applicants' rights thereto. Dependent claims 15 and 16, which correspond to claims 2 and 3 from the granted parent, have been added.

It is noted that the Examiner states that claim 5 is free of the art but makes no such comment regarding claims 3 and 4. However, claims 3 and 4 are not rejected over the art. All structures in claim 3 to 5 comprise "C" which is a compound of formula I and an essential element of the presently claimed compounds. These compounds of formula I have been found patentable in the granted parent. Since all of the present claims contains subject matter which was found to be patentable, the present claims must also be patentable over the art.

Regarding the "priority documents", there is only one, i.e., the parent application which has issued as U.S. 6,207,831.

The Abstract has been amended as in the parent application.

Regarding the figure legends, the Examiner is correct that the cited "Arrangement" represents guidelines. They are not mandatory. No amendment is necessary. It is noted that the parent issued with "Legends".

The text and figures have been amended as in the parent. Attached are formal drawings 2a, 2b, and 3. Original figure 2 has been re-drafted as 2a and 2b and figure 3 replaced to accommodate larger characters. The specification has been amended to reflect this change. It is requested that the replacement figures be entered.

A generic description (resins) for Tentagel has been added at page 8. It is noted, however, that the word does not appear to be protected by U.S. trademark.

The claims are rejected for various reasons under 35 USC 112 for lack of a written description. The rejection is traversed. The issues are discussed below.

(1) Specific linkage sites

Specific linkage sites between the moieties need not be recited since these can be readily known to one of ordinary skill in the art for the reasons which follow.

Moiety "A"

A is a solid support selected from standard materials applied in solid phase and solution phase organic chemistry. In the present application on page 1, under "Technical Field" it is stated:

"The present invention relates to the field of ultra high-throughput screening on the solid support and in homogeneous solution by a novel generic labeling technology. The new labeling technology is based on new chemically stable fluorophores, which possess reactive chemical functionalities for attachment to a solid support and subsequent start of combinatorial synthesis of compound libraries."

From this it is immediately evident that "A" must be such that it is be useful in screening techniques and in combinatorial synthesis of compound libraries. Such solid support and specific linking sites for linking chemical compounds to such solid support are known (see e.g. Fruechtel, J. S.; Jung, G. Organic chemistry on solid supports. Angew. Chem., Int. Ed. Engl. (1996), 35(1), 17-42). See also In the present application:

- Example 3B a "Rink amide resin", see e.g. Rink H. Solid-phase synthesis of protected peptide fragments using a trialkoxy-diphenyl-methyl ester resin; Tetrahedron Lett. (1987), 28(33), 3787-90, and
- Example 5B an aminoethyl-Tentagel resin, see e.g. Fruechtel, J. S.; Jung, G. Organic chemistry on solid supports. Angew. Chem., Int. Ed. Engl. (1996), 35(1), 17-42.

Therefore, it is deemed that a skilled man is immediately aware of the nature of "A" and the chemical binding to "B".

Moiety "B"

A linker is by definition a chemical moiety which connects two or more chemical entities. According to the present invention said linker must allow cleavage of the fluorescent conjugates for liberation of the D and C containing fragments. Such linkers are known and include benzyl, benzhydryl, benzhydryliden, trityl, xanthenyl, benzoin, silicon, or allyl based linkers (claim 13). Exemplified linkers are a benzhydryl group and a benzyl group in examples 3B, 5B, 6B, and 7B. It is immediately evident that the specific linkage sites between the moiety A and B must be such that the linker can be chemically reacted with a chemically reactive group which is part of a solid support. The specific linkage site is clearly dependent on the chemical nature of "A" and of "B". According to Example 3B this is a hydroxy group, according to examples 5B and 7B it is an amide group. The same is true for the specific linkage site between B and D, or B and C (e.g., which is according to example 3B conveniently an amide bond), or B and E (e.g. which is according to example 5B and 7B conveniently an amide bond).

Moiety "C"

Possible specific linkage sites are clearly defined in a compound of formula I and include those where a residue R₁ to R₆ is attached to a phenyl group in a compound of formula I.

Moiety "D"

A spacer is by definition a chemical moiety which connects two or more chemical entities and which provides space between two chemical entities which are attached via a spacer. A spacer D or D' includes according to the present invention α,ω -diamino-alkanes,

diaminocyclohexyl, bis-(aminomethyl)-substituted phenyl, α -amino- ω -hydroxy-alkanes, alkylamines, cyclic alkylamines, cyclic alkyldiamines, or amino acids without or with additional functionality in the side chain. Such a spacer has, e.g., two reactive groups which are suitable for connecting two chemical entities, e.g., two amine groups, amino and hydroxy groups, carboxy and amine groups, etc. The specific linkage site is thus, depending on the chemical nature of the spacer used, clearly defined for a man of ordinary skill.

Moiety "E"

"E" is defined as the compound to be investigated. A specific chemical linkage site is thus dependent on the chemical nature of "E" and this is immediately evident to a skilled man. In Example 3B "E" is biotin which is linked to D' via an amide bond. According to Example 5B and 7B "E" is an R-amine, wherein R is as defined in the table or R is cyclopropylmethyl and which is linked to "C" via an amide bond and to "B" via an amine bond. According to Example 6B "E" is Aryl-SO₃H, wherein Aryl is as defined in the Table which is linked to D' via an S(O₂)-N bond. However, the claims have amended to delete the E portion of the structures for formulae II and III, thus mooted this basis of rejection.

From the present application there is sufficient guidance and a skilled man is immediately aware of what chemical nature the specific linkage sites of A, B, C, D and D' can be. A more precise definition would improperly narrow the scope of protection to which the applicants are entitled, given the nature of the invention.

(2) Functional terms

The inventors are entitled to functional language in the claims because from the functional language a man of ordinary skill is immediately able to carry out the invention without undue experimentation.

re: Solid Support Claim 3 has been re-drafted as claim 12 and incorporates the wording from claim 4. Nothing is deemed to be vague or open-end about this list of supports, which are all standard materials which are used in solid phase and liquid phase organic syntheses. There is a broad range of solid supports and they exhibit a broad range of properties. For example, a support may be a solid in one phase (e.g., an ether) and be soluble in another phase, (e.g., an alcohol or water). (See, e.g., the references cited above; Bayer E., Mutter M. Liquid phase synthesis of peptides, Nature, 237:512-513, 1972; and Hermkens et al., Solid-Phase Organic Reactions II. Tetrahedron 53(16), 5643-5678, 1997.) The nature of these supports, how to form linkages to these supports, etc. are not vague or indefinite but rather are all matters of common knowledge to synthetic chemists.

re: B-portion of the claimed molecule

The arguments made above are incorporated herein.

re: Sufficiency of examples and Predictability in the art

First, the scope of claim 3 has been limited in the "C" portion to the compounds of formula I granted in parent US patent 6,207,831. Introduction of "C" makes conjugates of claims 3 to 5 fluorescent. Thus, as soon as a compound of claims 3 to 5 comprises the portion "C", each compound claimed has inevitably the function of having the advantageous fluorescent characteristics of "C". Thus, a man of ordinary skill has not only a reasonable expectation of success but will inevitably succeed in obtaining compounds having fluorescent characteristics when using his skill to prepare compounds as claimed in the present invention. Thus, the present scope is not an invitation to undue experimentation, as argued by the Examiner.

Furthermore, there are disclosed a total of 17 compounds (in Example 3B two compounds, in Example 5B ten compounds, in Example 6B four compounds, and in Example 7B one compound). Additionally, there are several representative examples for specific linkages between the different portions of the molecules claimed. Given the teachings in the specification, it is deemed that this is a sufficient number of examples to support the present, amended claim scope.

The claims are also rejected for various reasons under 35 USC 112 for lack of enablement. The rejection is traversed. The issues are substantially identical to those raised by the Examiner under the rejection for lack of written description and the responses thereto are similar to those above, which are incorporated herein. Again it is noted that fragment "C" has been limited in the amended claims to that which was granted in the parent application.

The claims are also rejected for various reasons under 35 USC 112 for indefiniteness. The rejection is traversed. It is again noted that many of the issues are substantially identical to those raised by the Examiner under the rejection for lack of written description and the responses thereto are similar to those above, which are incorporated herein. Again it is noted that fragment "C" has been limited in the amended claims to that which was granted in the parent application. Some of the issues are further discussed below.

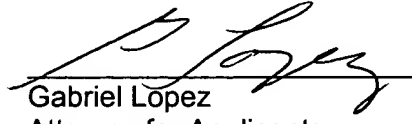
"Based" and "functionalized surfaces" These are not relative terms. They are only used in association with solid supports, which, as discussed above, are well known to the man of ordinary skill in the art of synthetic chemistry, especially since these are standard materials. Surfaces bearing reactive functional groups are commercially available

Attached is a replacement Declaration which is copied from the parent application, now U.S. 6,207,831

A two-month extension is hereby requested pursuant to 37 CFR §1.136(a) to respond to the Office Action dated April 9, 2002. Charge Deposit Account No. 19-0134 in the name of Novartis Corporation in the amount of \$400 for payment of the extension fee. The Commissioner is hereby authorized to charge any additional fees under 37 CFR §1.17 which may be required, or credit any overpayment, to Account No. 19-0134 in the name of Novartis Corporation.

Respectfully submitted,

Novartis Corporation
Patent and Trademark Dept.
564 Morris Avenue
Summit, NJ 07901-1027


Gabriel Lopez
Attorney for Applicants
Reg. No. 28,440
(908) 522-6933

encl: This page in duplicate
Figures 2a, 2b, & 3
Pages 8, 66, 79, and 80 showing changes
Declaration

Date: 9/9/02



SHEET SHOWING CHANGE

A-B-D-E-D'-C (Formula (III))

wherein

A is a solid support selected from standard materials applied in solid phase and solution phase organic chemistry (e.g. functionalized polystyrene based resins, polyacrylamide based polymers, polystyrene / polydimethylacrylamide composites, PEGA resins, polystyrene-polyoxyethylene based supports, Tentagel^{resins}, PEG-polystyrene graft polymeric supports, glass surfaces, functionalized surfaces, materials grafted with functionalized surfaces, or polyethylenglycol).

B is a linker allowing cleavage of fluorescent conjugates of formula (II-III) for liberation of the D-C-D'-E or D-E-D'-C fragment, respectively. B is selected from the known acid labile, base labile, light labile, redox-labile, and masked linkers applied in combinatorial synthesis, peptide synthesis, and oligonucleotide synthesis (e.g. benzyl, benzhydryl, benzhydryliden, trityl, xanthenyl, benzoin, silicon, or allyl based linkers).

C is a compound selected from formula (I)

D and D' are independently a bond or a spacer selected from α,ω -diamino-alkanes, diaminocyclohexyl, bis-(aminomethyl)-substituted phenyl, α -amino- ω -hydroxy-alkanes, alkylamines, cyclic alkylamines, cyclic alkyldiamines or amino acids without or with additional functionality in the side chain.

E is the molecule to be investigated e.g. a low molecular weight compound, a peptide, a protein, a carbohydrate, a nucleic acid, or a lipid bearing a functional group for attachment.

Conjugates of formula (II) can be generated via two independent protocols: (a) by *de novo* synthesis of molecule E, such incorporating a functional group of the spacer D' of the A-B-C-D' or A-B-D-C-D' fragment, respectively. (b) by attachment of a pre-built

SHEET SHOWING CHANGE

Legends to Figures:

(i) Figure 1

- (a) Absorption spectrum, of 25 μM **4e** in THF and fluorescence excitation spectrum (---). The small red shift in the fluorescence excitation spectrum is caused by monochromator deviations between the UV and the fluorescence instrument.
- (b) Fluorescence emission, 1 μM in THF, excitation at 342 nm.

(ii) ~~Figure 2~~ *Figs 2a and 2b*

- (a) – (i) Excitation and emission spectra of AIDA-conjugates **11**, **9**, and **8**, (in the graphical representation assigned as **BLI**, **BPI**, and **IPB**, respectively), and Avidin-Tryptophan, Avidin Lucifer Yellow and Avidin-BODIPY-FL, showing the overlap between tryptophan, BODIPY-FL and Lucifer Yellow emission and excitation, respectively.

(iii) Figure 3

Upper panel:

Fluorescence resonance energy transfer and ground state quenching in the **11** (BLI) (a) and **8** (IPB) (b) tryptophan avidin complexes. The curves are assigned by numbers 1-5.

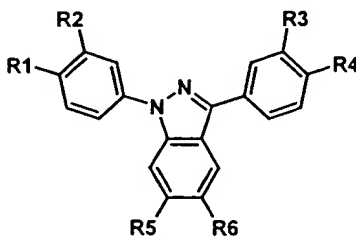
The difference spectra [$I(\mathbf{11} \text{ or } \mathbf{8}(\text{free})) + I(\text{avidin}(\text{free}))$] - $I(\mathbf{11-} \text{ or } \mathbf{8-avidin} \text{ Complex})$ are shown in curves 5.

The **11** fluorescence is quenched by about 25.5% by complexation in the avidin binding site. Approximately 62% of this total quenching effect is fluorescence

SHEET SHOWING CHANGE

Abstract

The invention relates to new fluorescent dyes of formula (I)



(Formula (I))

which can be used in high throughput screening both, on the solid phase as well as in homogeneous solution. ~~The new fluorescent dyes generically referred to as AIDA chemistry is suitable for various methods of solid phase and solution phase organic chemistry for synthesis of molecules to be investigated for therapeutic use in disease states. The molecules of therapeutic interest can be synthesized as fluorescent conjugates by two methods: (a) a solid support is loaded with a cleavable linker (acid-, base-, redox- or light sensitive) to which initially the fluorescent dye is attached. The dyes possess a second functionality, which serves as attachment point for spacer elements. The spacer bears a further functional group which is used as starting point of the synthesis of the molecules to be investigated; (b) the fluorescent dye can also be introduced as end-cap in the last synthesis step of a reaction sequence.~~

The dyes described in the invention are chemically stable under a broad range of reaction conditions usually applied in solid phase and solution phase organic chemistry. The conjugates emit fluorescence in the visible and UV-spectral range on excitation at wavelengths of their absorption. These fluorescence properties allow for multiple applications in fluorescence based processes for the identification of inhibitors of molecular interactions and for the identification of molecules which bind to target macromolecules like peptides proteins, nucleic acids, carbohydrates etc.

SHEET SHOWING CHANGE

The fluorescence detection technologies used for monitoring binding of AIDA-conjugated compounds to macromolecules include conventional macroscopic techniques (ensemble averaging) which detect changes in fluorescence intensity, anisotropy(polarization), fluorescence resonance energy transfer, fluorescence lifetime, rotational correlation time as well as one- and twodimensional single molecule spectroscopic techniques (SMS).

Uses of the dye include solid phase and solution phase organic chemistry, low molecular weight compound labelling, peptide labelling, protein labelling, optical spectroscopy and fluorescence. Synthesis of functionalized dyes and of dye conjugates (on solid support and in solution) are disclosed.